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Clinicopathologic analysis and prognosis of gastrointestinal stromal tumors located in upper gastrointestinal tract

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이 논문을 의학석사 학위논문으로 제출함

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Clinicopathologic analysis and prognosis of gastrointestinal stromal tumors located in upper gastrointestinal tract

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Abstract

Background: Gastrointestinal stromal tumors (GISTs) are most common mesenchymal neoplasm in the digestive tract. There are many reports for gastric GISTs, but are only a few clinicopathologic series including duodenum and small intestinal GISTs. The objectives of this study were to analyze the clinicopathologic features, to explore the prognostic factors in patients with primary GISTs located in upper gastrointestinal (GI) tract, and to clarify the clinicopathologic features and the prognosis of GISTs located in upper GI tract differ in primary tumor location as duodenum, small intestine, and stomach.

Methods: 297 patients from a total of 343 patients with GIST located in duodenum (n = 40, 13.5%), small intestine (n = 61, 20.5%) or stomach (n = 196, 66.0%) underwent surgical resection between 1996 and 2010. We analyzed clinicopathologic feature, immunohistochemical aspects, surgical outcome, and prognostic factors.

Results: Five-year survival rate (5YSR) in patients with duodenum, small intestine, and stomach were 66.6%, 80.8%, and 91.0%, respectively (p = 0.002). After univariate analysis, adverse prognostic factors in patients with GIST were revealed as male gender (5YSR 82.9 vs. 89.6%, p = 0.036), R2

resection (5YSR 36.7 vs. 90.5%, $p < 0.001$), initial low serum hemoglobin (Hb) level (< 12 mg/dl) (5YSR 76.9 vs. 95.0%, $p = 0.002$), advanced T stage (5YSR T4 69.1, T3 87.1, T2 95.3, T1 100%, $p < 0.001$), high mitotic counts (> 5/ 50 HPFs) (5YSR 75.7 vs. 96.9%, $p < 0.001$), mucosal involvement (5YSR 75.8 vs. 93.0%, $p = 0.002$), presence of necrosis (5YSR 74.9 vs. 92.2%, $p = 0.002$), presence of mucosal ulcer (5YSR 80.0 vs. 89.4%, $p = 0.034$), and the expression of S100 (5YSR 59.5 vs. 91.9%, $p = 0.003$). After multivariate analysis, male gender (HR = 7.196, $p = 0.043$), R2 resection (HR = 21.820, $p = 0.019$), and the expression of S100 (HR =15.622, $p = 0.023$) were identified as independent adverse prognostic factors in patients with GIST. In addition, advanced T stage (HR = 3.895, $p = 0.061$), mucosal involvement (HR = 4.448, $p = 0.073$), no use of adjuvant imatinib treatment (HR = 2.683, $p = 0.060$) were revealed adverse prognostic factors with statistically marginal significance. In subgroup analysis with limited to primary duodenal and small intestinal GISTs, additional adverse prognostic factors were identified, such as, combined epitheloid cell component (5YSR 61.5 vs. 87.2%, $p = 0.009$), and immunopositivity of PDGFRA (5YSR 36.4 vs. 77.2%, $p = 0.043$). In the point of comparison of biologic potential, the rate of progressive disease was greater in duodenal or small intestinal GIST than gastric GIST (42.2% vs. 13.0%, $p < 0.001$).

Conclusion: Primary duodenal and small intestinal GISTs differ from primary gastric GISTs in terms of clinical, pathological, and immunohistochemistrical aspects. In case of duodenal or small intestinal GIST, surgical resection should be considered even if relatively low risk group.

Keywords: Gastrointestinal stromal tumors, clinicopathologic features, prognostic factors

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Introduction

Gastrointestinal stromal tumors (GISTs) represent the most common KIT-driven mesenchymal tumors of the gastrointestinal (GI) tract showing differentiation along the line of interstitial cell of Cajal.[1-4] The morphologic classification of these lesions has evolved over time, and molecular analysis has led to a better understanding of their nature.[5]

GISTs are more frequent in the stomach (approximately 50- 60%) and in the small bowel (25- 30%). Duodenum or other sites are comparatively much rarer anatomic locations accounting for approximately 10%.[1, 6, 7] Due to the relatively low incidence compared to stomach, the characteristics and surgical prognosis of patients with primary small intestinal GIST, especially duodenal GISTs, have not been well clarified.

Recently, recognition of GIST in order to enable the patients for specific targeted therapy has become important. This process is aided by understanding the potential occurrence of GIST in almost any segment of the GI tract. It is also helpful to know the morphologic variation of GIST at different sites and application of immunohistochemical markers.

This study is aimed to analyze the clinicopathologic features, to explore the prognostic factors in patients with primary GISTs located in upper GI tract,

and to clarify the clinicopathologic features and the prognosis of GISTs located in upper GI tract differ in primary tumor location as duodenum, small intestine, and stomach.

Patients and methods

Study population

With institutional review board approval, 297 patients among a total of 343 patients visited Seoul National University Hospital with primary duodenal, small intestinal, or gastric GIST who underwent resection have been entered into a prospectively maintained database between 1996 and 2010. Among them, 40 patients (13.5%) had duodenal GISTs, 61 patients (20.5%) small intestinal GISTs, and 196 patients (66.0%) gastric GISTs (Figure 1).

Surgical resection

Two- hundred ninety-seven patients among a total of 343 patients had resection. Of these patients, 40 patients with duodenal GIST got either local resection or pancreaticoduodenectomy. Sixty-one patients with small

intestinal GIST had been performed mostly segmental resection of affected intestinal segment. The patients with gastric GIST (n= 196) had been performed partial or total gastrectomy. Surgical procedure was customized mainly to the size, location, and extent of disease through macroscopic assessment. Routine lymphadenectomy was not performed. Margin status was assessed in the standard manner.

Comparison of clinicopathologic variables in patients with GIST and patients follow- up

Clinical variables were evaluated with age, sex, R status, initial serum CEA/ CA 19-9 level, initial serum hemoglobin level, and main symptom among 297 patients with resected GIST. Based on pathologic report, pathologic variables, such as, size, mitosis (/ 50 High Power Fields; HPFs), mucosal involvement, presence of muscle invasion, necrosis, and mucosal ulcer were evaluated. Especially, after review of pathology by single pathologist, additional parameters with cellularity, cellular atypism, desmin, nuclear palisades, and epitheloid cell component were analyzed in patients with duodenal and small intestinal GIST (Figure 1). Histologic findings were described in accordance with the 7th edition TNM staging of the American

Joint Committee on Cancer (AJCC).[8]

Patients were followed regularly in outpatient clinics every 3–6 months, and follow-up information for all 297 patients was obtained. The sites of initial disease recurrence were determined from cross-sectional imaging studies or endoscopy. Overall survival was analyzed from the date of surgical resection to the date of death from all causes. The causes of death were determined from the medical records. The follow-up period was defined as the interval between the date of surgical resection and that of the last follow-up.

Immunohistochemical staining

Most of tumors were evaluated for CD117 expression by immunohistochemistry to confirm the diagnosis. CD34, smooth muscle actin, and S100 in most of patients with GIST located in upper GI tract were also evaluated for differential diagnosis.

Ki-67 and PDGFRA were evaluated in patients with duodenal and small intestinal GIST to explain the prognosis. Formalin-fixed and paraffin embedded blocks were cut into sections of 5-mm thickness. These sections were pretreated according to the requirements of primary antibodies. Primary

antibodies applied were listed below: mouse anti-human Ki-67 monoclonal antibody (1:100; DAKO), and rabbit anti-human PDGFRA monoclonal antibody (1:200; Santa- cruz). Subsequent development of the antibody reaction was done by Lab Superbiochip (Lab Superbiochip Corp., Seoul, South Korea). Bond polymer Refine Detection kit (Leica, Inc.) was applied for detection kit according to the instruction manual. A tissue section of human cancer that was known to contain the marker served as a positive control in each course of staining. In negative controls, the primary antibody was omitted. Immunohistochemical staining for Ki-67 and PDGFRA was evaluated by estimating 50 HPFs. Tumor nuclei staining were counted and a cut-off at 20% positivity was used for analysis. Ki-67, the number of cells with brownish nuclei per 1,000 cells on HPFs was counted by Scanscope Slide Scanning Systems and Spectrum Plus Software (Aperio Digital Pathology Environment Technology, Vista, CA) to determine the Ki-67 index (%). Immunoreactivity for PDGFRA was evaluated by estimating 50 HPFs. Tumor nuclei staining were counted and a cut-off at 10% positivity was used for analysis.

Statistical analysis

The data was analyzed using SPSS ver. 19.0 (SPSS Inc., Chicago, IL). Continuous and normally distributed variables are presented as means ± standard deviations. Continuous parameters in each group were compared using the independent t test, and categorical parameters using the $\chi 2$ test or Fisher's exact test. Medical records and survival data were obtained for all patients. Survival curves were constructed using the Kaplan–Meier method and differences in survival were evaluated using the log-rank test. Multivariate analysis for prognostic factors was using Cox proportional hazards model. Probability (p)- values of 0.05 or less were considered statistically significant, while p from more than 0.05 to 0.10 were considered marginally significant.

Results

Clinical variables in patients with GIST

Clinical findings in patients with GIST after surgical resection are listed in table 1. Mean age was 53.9 (range 21- 84) years and male to female ratio was 1.0: 1. Resection status were classified as R0 (n = 269), R1 (n = 6), and R2 (n = 22). Initial hemoglobin (Hb) level according to the primary tumor

site was 13.5 ± 1.8 mg/dl in duodenal GIST, 11.6 ± 2.7 mg/dl in small intestinal GIST, 12.7 ± 2.4 mg/dl in gastric GIST (p = 0.008). The most common presenting symptom was epigastric discomfort (n = 58, 19.5%); others included GI bleeding (n = 53, 17.8%), abdominal pain (n = 53, 17.8%), and palpable abdominal mass (n = 16, 5.4%). A hundred four patients (35.0%) were asymptomatic and diagnosed occasionally through routine examination. Median follow-up was 56.0 (range 0- 167.0) months (Table1).

Pathologic characteristics in patients with GIST located in upper GI tract

The mean size of the 297 primary resected tumors was 6.7 ± 4.9 cm. Mean mitotic counts was 17.5 ± 43.5 /50 HPFs. All patients with duodenal GIST had muscle invasion (n = 26), whereas those with small intestinal GIST got 40 patients (97.6%), and those with gastric GIST got 131 patients (84.5%). All tumors except 1 gastric GIST expressed CD117. Gastric GIST had more expressed CD34 (n = 155, 96.3%) than duodenal GIST (n = 25, 80.6%) and small intestinal GIST (n = 36, 70.6%) (p < 0.001). The expression of smooth muscle actin of duodenal GISTs (n = 11, 33.3%) and small intestinal GISTs (n= 15, 30.6%) was more frequent than that of gastric GISTs (n= 24, 14.5%) (p = 0.006). The expression of S100 of duodenal GISTs (n= 6, 17.6%) and

small intestinal GISTs (n= 8, 15.1%) was more frequent than that of gastric GISTs (n= 8, 4.7%) (p = 0.008) (Table 2).

Immunohistochemical variables in patients with GIST

The examples of immunohistostaining with Ki-67 and PDFGRA were followed with Figure 2.

Survival analysis in patients with GIST located in upper GI tract

Overall 5-year survival rate (5YSR) of GIST located in upper GI tract after resection was 86.0% (Figure 3). In the univariate analysis, the patients with gastric GIST showed the most favorable prognosis (5YSR = 91.0%), then those with small intestinal GIST (5YSR = 80.8%), and those with duodenal GIST did the worst prognosis (5YSR = 66.6%) (p = 0.002) (Figure 4, Table 3). The other adverse prognostic factors in patients with GIST were revealed as male gender (5YSR 82.9 vs. 89.6%, p = 0.036), R2 resection (5YSR 36.7 vs. 90.5%, p < 0.001), initial low serum Hb level (< 12 mg/dl) (5YSR 76.9 vs. 95.0%, p = 0.002), advanced T stage (tumor size)[8] (5YSR T4 69.1, T3 87.1, T2 95.3, T1 100%, p < 0.001), high mitotic counts (> 5/ 50 HPFs)

(5YSR 75.7 vs. 96.9%, $p < 0.001$), mucosal involvement (5YSR 75.8 vs. 93.0%, $p = 0.002$), presence of necrosis (5YSR 74.9 vs. 92.2%, $p = 0.002$), presence of mucosal ulcer (5YSR 80.0 vs. 89.4%, $p = 0.034$), and the expression of S100 (5YSR 59.5 vs. 91.9%, $p = 0.003$) (Table 3).

After multivariate analysis, there were several independent adverse prognostic factors with male gender (HR = 7.196, $p = 0.043$), R2 resection (HR = 21.820, $p = 0.019$), and the expression of S100 (HR =15.622, $p = 0.023$). In addition, advanced T stage (HR = 3.895, $p = 0.061$), mucosal involvement (HR = 4.448, $p = 0.073$), no use of adjuvant imatinib treatment were revealed independent adverse prognostic factor with statistically marginal significance (Table 4).

Survival analysis with use of adjuvant imatinib treatment

Among high risk patients (n = 188, tumor size ≥ 5cm, mitotic counts > 5/ 50HPF) according to NIH classification scheme, 75 patients received imatinib as adjuvant therapy. The median disease-free duration of follow-up in patients with imatinib was significantly longer than that without imatinib (53 vs. 25 months, $p = 0.003$) (Figure 5). As mentioned above, no use of adjuvant imatinib treatment were revealed independent adverse prognostic

factor with statistically marginal significance (Table 4).

Subgroup survival analysis confined to duodenal or small intestinal GISTs

After pathologic review, additional several pathologic variables were evaluated in patients with duodenal and small intestinal GISTs. As a result, combined epitheloid cell component (5YSR 61.5 vs. 87.2%, $p = 0.009$) was identified statistically significant adverse prognostic factors (Table 5). After additional immunohistochemical staining with PDFGRA and Ki-67, only PDGFRA had an adverse prognostic value (5YSR 36.4 vs. 77.2%, $p = 0.043$) (Table 5, Figure 6)

Risk stratification of tumor progression compared duodenal/ small intestinal GISTs to gastric GISTs

According to the Miettinen-Lasota/Armed Forces Institute of Pathology classification system[7], disease progression by tumor location was listed with Table 6. The rate of disease progression of duodenal or small intestinal

GISTs was higher than that of gastric GISTs (42.2% vs. 13.0%, $p < 0.001$) (Table 6).

Discussion

GIST can be considered as neoplastic derivatives of Cajal cells or their precursors. Cajal cells are a small KIT-positive spindle cell population especially located around the myenteric plexus.[3, 9, 10] Pathologically, the diagnosis of GIST relies on the variable combination of morphology, immunohistochemistry (CD117) and, in selected cases, on molecular analysis.[1] The pathology report plays a key role in the therapeutic planning of patients affected by GIST. Critical issues are represented by accurate morphologic diagnosis implemented by relevant immunohistochemical stains, assessment of the risk of progression.[1] The standard treatment for primary, localized GIST is surgical resection achieving negative margins (R0 resection). Survival after surgical resection of GISTs ranges from 48% to 80% at 5 years.[11-14] In the present study, 5YSR after surgical resection in patients with GIST located in upper GI tract was 86.0% (Figure 3)

GISTs occur throughout the GI tract, usually in persons > 50 years of age with a median age of 62–63 years, although a clinicopathologically

distinctive pediatric GIST subgroup exists.[3, 5-7, 15] In our study, mean age of study population was about 54 years, this result can be caused not only relatively earlier onset of these tumors than Western countries but also incidental finding by wide application of endoscopy. (Table 1)

GISTs were known as to equally affect female and male patients,[3, 15, 16] as similar in this study (Table 1). Interestingly, some authors reported that male gender was one of the poor survival factors in patients with GIST.[11, 17] In this study, we could find male gender as independent poor prognostic factor (Table 3, Table 4).

The spectrum of clinical presentation is broad and is mainly related to tumor size. Small tumors are usually identified incidentally during endoscopy or abdominal surgery, whereas large tumors will generally be associated with some form of GI bleeding either acute bleeding, such as hematemesis, or chronic, insidious bleeding, manifested clinically by fatigue and weakness secondary to iron deficiency anemia,[5, 6, 15] or mass effect including early satiety, and bloating.[3] In this study, anemia also played adverse prognostic effects in patients with GIST after univariate analysis (5YSR 76.9 vs. 95.0%, p = 0.002; Table 3). But we could not reveal initial low Hb level as independent adverse prognostic factor after multivariate analysis (Table 4).

As mentioned above, the standard treatment for primary, localized GIST is surgical resection achieving negative margins because R2 surgery was adverse prognostic value in patients with GIST.[18, 19] In this study, R2 resection was identified as independent adverse prognostic factor (HR = 21.820, $p = 0.019$; Table 4).

Despite Yang et al suggested that the patients with completely resected primary duodenal GIST seem to have a more favorable prognosis,[20] many studies have shown that small intestinal GISTs including duodenal GIST had the worse prognosis than gastric GIST.[15, 21-25] This present study added the evidence of non-gastric location of GIST as an adverse prognostic factor after univariate analysis (Figure 4, Table 3).

Grossly, the size of GISTs ranges from 1 to 35 cm, with a median size of 6.7cm (Table 2). There is general agreement that tumor size is one of the most important prognostic factors in GISTs.[3, 6, 15, 16, 25, 26] In this study, size of GIST had a prognostic value (Table 3, Table 4).

Mitotic activity of GISTs is generally low, however, approximately 25% of cases exhibits more than 10 mitoses/ 50 HPFs.[1] Mitotic index is also one of the main prognostic variables used in risk assessment and has been documented as the most important variable in several instances.[3, 19, 26-28] Similarly, we could find high mitotic counts (> 5/ 50 HFPs) as poor

prognostic factor (5YSR 75.7 vs. 96.9 %, $p < 0.001$) (Table 3).

In the present study, revealed other poor prognostic factors were mucosal involvement of tumors, mucosal ulcer, and coagulative necrosis (Table 3, Table 4) in accordance with other previous report. [29] So these factors are important gross parameters that should be recorded in every patient with GIST.

S100 protein is also well-known epithelial markers for the differential diagnosis for GIST with other mesenchymal tumors with staining up to 5%.[3, 16, 30-32] but there was rare study reporting its prognostic value in patients with GISTs excepts previous Korean reports.[29, 33] Interestingly, our study had result with S100 expression in patients with GISTs as independent adverse prognostic factor (Table 3, Table 4). As a result, it may be unique characteristics of Korean population with GIST.

GISTs are now understood as generally KIT-positive, and this information has been the basis of the new KIT tyrosine kinase inhibitor drugs, imatinib mesylate and second and third generation inhibitors now routinely used in the treatment of metastatic and unresectable GISTs. [2, 3, 24, 31, 34] The overall prognosis of GISTs, including this study (median disease-free survival 53 vs. 25 month, $p = 0.003$; Figure 5), has changed dramatically since the introduction of kinase inhibitor therapy. Recently, a trial of adjuvant imatinib

versus placebo for primary R0-resected intermediate and high-risk GISTs was closed early because imatinib significantly improved recurrence-free survival.[35]

On histology, about 70% of GISTs are composed of spindle cells, 20% of epithelioid cells, and the remaining 10% of mixed cell types.[3, 5, 16, 21] Some studies reported that when they arise in the small bowel, epithelioid GISTs have a tendency to adopt a so-called paraganglioma- like pattern, which has been associated with unfavorable prognosis.[5, 6, 29] Our study also had similar result (5YSR 61.5 vs. 87.2%, $p = 0.009$) (Table 5). As a result, despite a few report insisted epithelioid GIST had no clinical relevance[1], histologic type of small intestinal GISTs including duodenal GISTs may play a prognostic role.

It is known that PDGFRA strong immunopositivity is often observed in PDGFRA mutated cases, however Dei Tos et al suggested that this finding need to confirm further validation.[1] Also, Kern et al reported that expression of PDGFRA is not independent prognostic factors after curative resection of primary GIST.[36] But in this study, the expression of PDGFRA confined to duodenal and small intestinal GISTs was an adverse prognostic factor (5YSR 36.4 vs. 77.2%, $p = 0.043$; Table 5, Figure 6). So we suggest that more observation is needed to draw any conclusions of usefulness of PDGFRA immunostaining because this adverse prognostic effect on survival can be

caused not only true adverse effect but also by type II error.

Ki-67 index is one of the most frequent prognostic markers as negative predictor studied in the literature on GISTs.[37-45] In this study, after pathologic review, we re-evaluated the prognostic meaning of Ki-67 index with additional immunohistochemical staining in patients with duodenal and small intestinal GIST (Figure 1, Figure 2), but we could not find statistical difference in survival between high and low Ki-67 index (Table 5). Nevertheless, we believe Ki-67 index may have prognostic effect because this result could be caused by selection bias confined to duodenal and small intestinal GIST. For confirmation of this conflict, the more observational studies including gastric GISTs are needed.

Risk stratification systems assist in determining the risk of disease recurrence in individual patients with GIST, so disease management can be personalized. Determining the likelihood of GIST recurrence after surgical resection has a direct impact on management decisions, such as the frequency of patient follow-up and whether adjuvant tyrosine kinase inhibitor therapy should be considered. Therefore, risk stratification systems that assist in determining the risk of recurrence have been developed and are more commonly used than conventional staging schemes in GIST management.[26] The risk of relapse is estimated on the basis of mitotic rate,

tumor size, tumor site, surgical margins and whether tumor rupture has occurred. Tumor size and mitotic count are considered by the 2002 Consensus risk classification.[1, 21] A more recently proposed risk classification incorporates primary tumor site in addition to the mitotic count and tumor size.[7] In particular, it reflects the fact that gastric GISTs have a better prognosis than small bowel or duodenal GIST. [1, 7, 15, 46] In the present study, the prognosis of duodenal or small intestinal GIST was poorer than that of gastric GISTs (Figure 4, Table 3). It may be because duodenal/ small intestinal GISTs showed larger size, frequency of mucosal involvement, and higher expression of S100 than gastric GISTs. As a result, rate of progressive disease in patients with duodenal/ small intestinal GIST was higher than that with gastric GIST (42.2 vs. 13.0%, $p = 0.001$; Table 6).

There are limitations in our study. At first, our data did not contain mutation analysis for KIT or PDGFRA. For evaluation of GIST, mutational analysis of specific gene is important.[37, 47] For this reason, we have a plan to future additional genetic analysis for KIT/ PDGFRA mutational status. At second, we performed additional immunohistochemical staining of PDGFRA/ Ki-67 confined to duodenal/ small intestinal GISTs. It may cause possible selection bias. To solve this problem, future prospective study containing all of the GISTs with any site of GI tract will be needed.

Conclusions

Primary duodenal and small intestinal GISTs differ from primary gastric GISTs in terms of clinical, pathological, and immunohistochemistrical aspects. The patients with duodenal or small intestine GIST had poorer prognosis than those with gastric GIST. In case of duodenal or small intestinal GIST, aggressive treatment including surgical resection should be considered even if relatively low risk group.

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Tables

Table 1. Clinical characteristics of the 297 patients with GIST after resection

	Duodenal (n = 40)	Small intestinal (n = 61)	Gastric (n = 196)	Total (n = 297)	*p*
Age (yrs)	51. ± 13.8 (21- 77)	53.4 ± 13.2 (23- 80)	56.7 ± 11.1 (22- 84)	53.9 ±5 6.6 (21- 84)	0.012
Sex (M:F)	20: 20	34: 27	97: 99	151: 146	0.691
R status (R0: R1: R2)	36 : 0: 4	45 : 5: 11	188 : 1: 7	269: 6: 22	<0.001
Initial CEA level	1.3 ± 0.7	1.5 ± 1.0	1.5 ± 0.9	1.5 ± 0.9	0.867
Initial CA 19-9 level	8.9 ± 6.6	8.3 ± 8.6	7.9 ± 7.7	8.1 ± 7.7	0.918
Initial Hb level	13.5 ± 1.8	11.6 ± 2.7	12.7 ± 2.4	12.6 ± 2.5	0.008
Presentation (n, %)					
Incidental finding	12 (30.0)	11 (18.0)	81 (41.3)	104 (35.0)	<0.001
Epigastric symptom	1 (2.5)	0	57 (29.1)	58 (19.5)	

Abdominal pain	12 (30.0)	21 (34.4)	20 (10.2)	53 (17.8)	
fever	2 (5.0)	0	1 (0.5)	3 (1.0)	
Weight loss	1 (2.5)	1 (1.6)	2 (1.0)	4 (1.3)	
G-I bleeding	10 (25.0)	19 (31.1)	24 (12.2)	53 (17.8)	
Abdominal mass	2 (5.0)	8 (13.1)	6 (3.1)	16 (5.4)	
others	0	1 (1.6)	5 (2.6)	6 (2.0)	
F/U (median, mo)	42(4- 138)	54 (0- 148)	62 (0- 167)	56 (0- 167)	0.281

Table 2. Pathologic characteristics of the 297 patients with GIST located in upper GI tract after resection

	Duodenal (n = 40)	Small intestinal (n = 61)	Gastric (n = 196)	Total (n = 297)	*p*
Size (cm)	6.6 ± 5.3	8.4 ± 4.7	6.2 ± 4.7	6.7 ± 4.9	0.016
Mitosis (/50 HPFs)	34.9±86.8	12.6 ± 16.6	15.5 ± 34.8	17.5 ± 43.5	0.025
Mucosal involvement (%)	13/ 26 (50.0)	17/ 43 (39.5)	50/ 159(31.4)	80/ 228(35.1)	0.147
Muscle invasion (%)	26/ 26 (100)	40/ 41 (97.6)	131/ 155(84.5)	197/ 222(88.7)	0.010
Necrosis (%)	6.5 ± 13.3	9.2 ± 14.7	9.7 ± 17.6	9.1 ± 16.3	0.563
Mucosal ulcer (%)	10/ 33 (30.3)	9/ 39 (23.1)	42/ 151 (27.8)	61/ 223 (27.4)	0.771
KIT (CD117) (n, %)	30/ 30 (100)	55/ 55 (100)	149/ 150 (99.3)	234/ 235 (99.6)	0.752
CD34 (n, %)	25/ 31 (80.6)	36/ 51 (70.6)	155/ 161 (96.3)	216/ 243 (88.9)	<0.001
Smooth muscle actin (%)	11/ 33 (33.3)	15/ 49 (30.6)	24/ 166 (14.5)	50/ 248 (20.2)	0.006

S100 (%)	6/ 34 (17.6)	8/ 53 (15.1)	8/ 169 (4.7)	22/ 256 (8.6)	0.008

Table 3. Survival analysis in patients with GIST located in upper GI tract

Variable		N	Median (Mo)	5YSR (%)	P
Age	< 60 / ≥ 60	173/ 124	63/ 42	87.9/ 83.0	0.213
Sex	Male/ Female	151/ 146	53/ 57	82.9/ 89.6	0.036
R status	R0/ R1/ R2	269/ 6/ 22	57/ *NC/ 43	90.5/ *NC/ 36.7	< 0.001
Location	Duodenum/ #SB/ Stomach	40/ 61/ 196	42/ 54/ 62	66.6/80.8/91.0	0.002
Initial Hb level (mg/dl)	<12/ ≥12	79/ 159	52/ 67	76.9/ 95.0	0.002
T stage (Size)	T1/ T2/ T3/T4	16/130/ 87/54	*NC/ 53 / 57/59	100/95.3 /87.1/69.1	< 0.001
N stage	N0/ N1	289/ 6	56/ 73	87/ 80	0.410
Mitosis (/50ᵉHPFs)	≤5/ >5	154/ 136	58/ 53	96.9/ 75.7	< 0.001
Mucosal involvement	No/ Yes	148/ 80	57/ 43	93.0/ 75.8	0.002

Muscle invasion	No/ Yes	25/ 197	79/ 53	92.9/ 86.8	0.246
Necrosis	No / Yes	122/ 99	57/ 55	92.2/ 74.9	0.002
Mucosal ulcer	No / Yes	162/ 61	58/ 55	89.4/ 80.0	0.034
CD34	No / Yes	27/ 216	62/ 58	88.2/ 88.9	0.369
Smooth muscle actin	No / Yes	198/ 50	56/ 62	89.3/ 81.6	0.425
S100	No / Yes	234/ 22	56/ 55	91.9/ 59.3	0.003

*NC; not calculated, [#]SB; small intestine, [ε]HPF; high power field

Table 4. Multivariate analysis in patients with GIST located in upper GI tract

Multivariate analysis: Cox proportional hazard analysis

	HR	95% CI	P
Male gender	7.196	1.090- 47.520	0.040
Macroscopic remnant tumor (R2)	21.820	1.663- 286.291	0.019
Location (*D > SB > S)	2.226	0.347- 14.263	0.399
Initial low Hemoglobin level (< 12mg/dl)	1.964	0.939- 16.163	0.534
T stage (size)	3.895	0.605- 4.590	0.061
Mitosis (/ 50 [ε]HPF)	1.198	0.561- 28.677	0.847
Mucosal involvement	4.448	0.871- 22.721	0.073
Necrosis	1.339	0.247- 7.261	0.985
Mucosal ulcer	5.990	0.634- 56.571	0.118
S100	15.622	1.464- 166.676	0.023
[#]No use of adjuvant Gleevec	2.683	0.958- 7.511	0.060

**D; duodenum, SB; small intestine, S: stomach*

[ε]HPF; high power field

[#] confined to high risk patients (≥ size 5cm, mitosis > 5/ 50HPFs)

Table 5. Subgroup survival analysis confined to patients with duodenal or small intestinal GIST

Variables		**N**	**Median (Mo)**	**5YSR (%)**	**P**
*Cellularity	0+1/ 2+3	10/ 69	NC/ 63	NC/ 76.9	0.557
#Atypia	0+1/ 2+3	21/ 61	67/ 56	93.3/ 73.9	0.076
Desmin	No/ Yes	51/ 7	62/ 79	85.7/ 60.0	0.341
Skenoid fiber	No / Yes	47/ 24	60/ 71	72.2/ 89.3	0.204
Nuclear palisades	No / Yes	51/ 20	66/ 51	78.2/ 76.1	0.908
Epitheloid cell component	No/ Yes	48/ 27	65/ 53	87.2/ 61.5	0.009
εPDGFRA	No/ Yes	40/ 11	48/ 43	77.2/ 36.4	0.043
Ki-67 index (%)	< 3/ ≥3	45/ 22	42/ 58	73.9/ 67.5	0.856

** 0: absent, 1: low, 2: moderate, 3: high*

 # 0: absent, 1: mild, 2: moderate, 3: marked

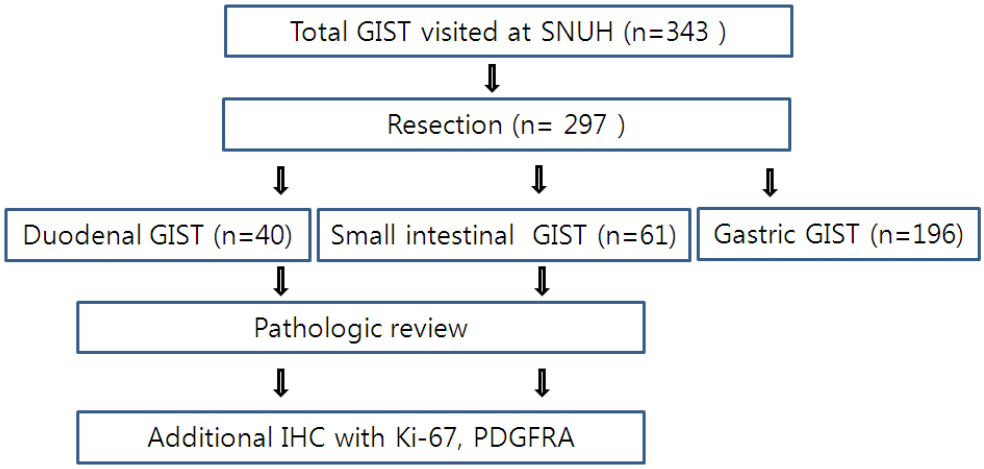
εPDGFRA; platelet-derived growth factosr receptor α

Table 6. Disease progression by tumor location according to M-L/AFIP classification system [6, 15]

	Rate of progressive disease (%)		*p*
Risk group	**Duodenal or Small intestinal**	**Gastric**	
1	0	0	
2	9.5	0	
3 a	15.8	3.7	
3 b	25.0	0	
4	-	0	
5	45.5	5.6	
6 a	47.1	29.2	
6 b	61.1	61.9	
Total	42.2	13.0	< 0.001

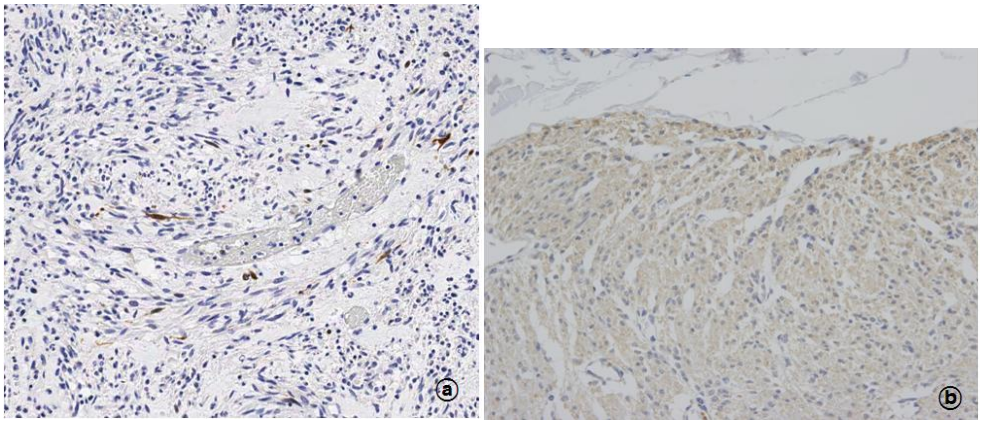
Figures

Figure 1. Patients flow of 297 patients who underwent surgical resection with GIST



IHC; immunohistochemistry, PDGFRA; platelet-derived growth factor receptor α

Figure 2. Photograph of the representative IHC of GISTs



ⓐ Diffuse positive staining of Ki67 of duodenal GIST (X 400)

ⓑ Diffuse positive staining of PDGFRA of small intestinal GIST (X 400)

Figure 3. Survival curve of resected GIST located in upper GI tract (n = 297)

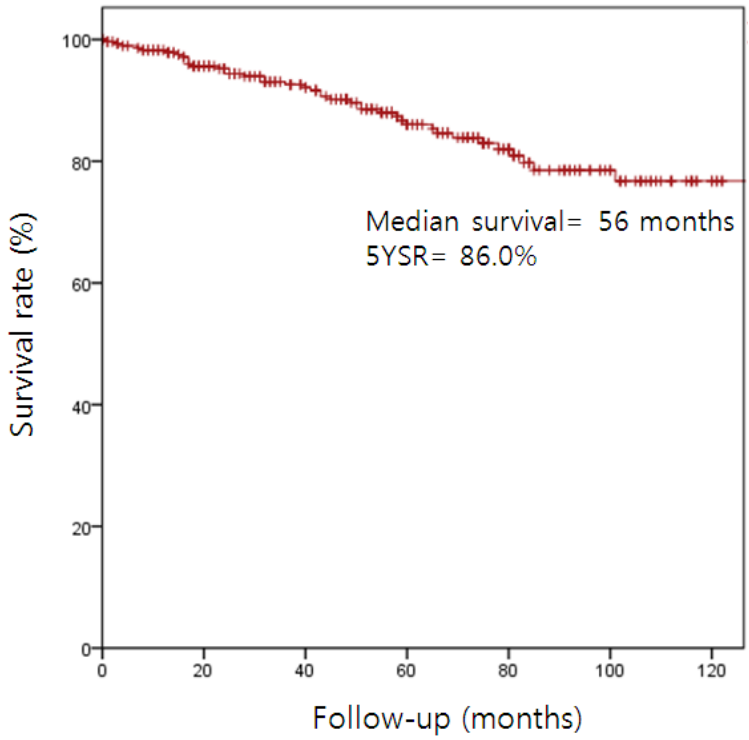
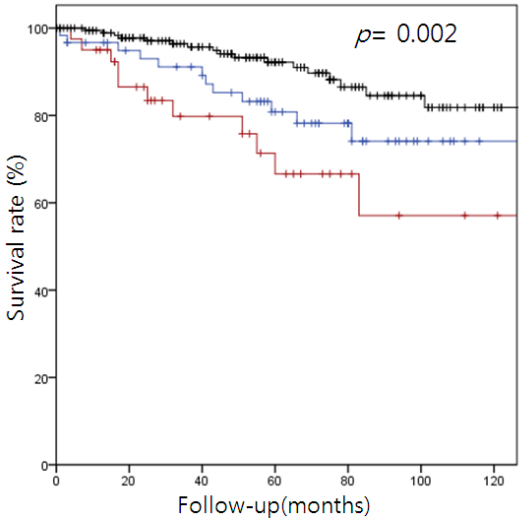
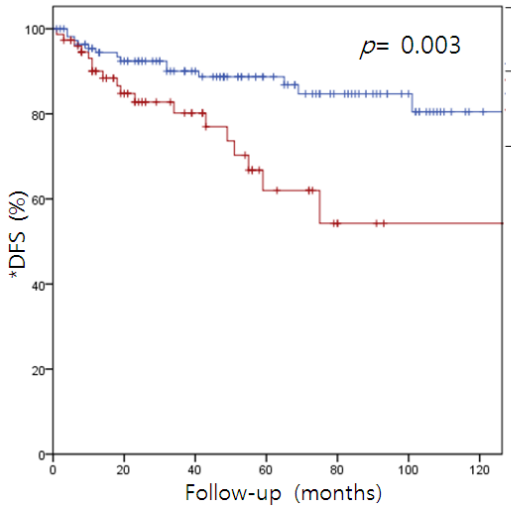


Figure 4. Survival according to location of primary tumor



location	Median (months)	5YSR (%)
Duodenal (n= 40)	42	66.6
Small Intestinal (n= 61)	54	80.8
Gastric (n= 196)	62	91.0

Figure 5. Survival according to adjuvant imatinib treatment

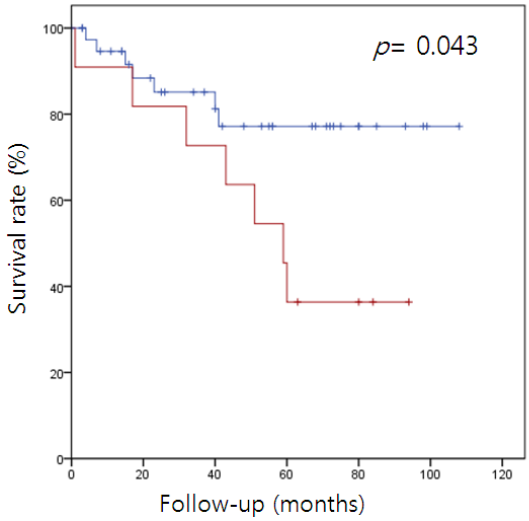


Imatinib	Median *DFS (months)	#5YDFSR (%)
No (n= 113)	25	62.0
Yes (n= 75)	53	88.7

**DFS; disease-free survival*

#5YDFSR; 5- year disease-free survival rate

Figure 6. Survival curve according to *PDFGRA in patients with duodenal or small intestinal GIST



PDGFRA	Median (months)	5YSR (%)
No (n= 40)	48	77.2
Yes (n= 11)	43	36.4

***** *PDGFRA; platelet-derived growth factor receptor* α

국문초록

상부위장관에 발생한 위장관간질종양의 임상병리학적 분석 및 예후

서울대학교 대학원

의학과 외과학 전공

한 인 웅

<목적> 위장관간질종양은 소화기계에서 발생한 가장 흔한 중배엽 기원 종양이다. 그러나 위장에서 발생한 종양과 달리, 십이지장 및 소장에서 발생한 위장관간질종양에 대한 임상병리학적 연구는 소수에 불과하다. 본 연구의 목적은, 상부위장관에 발생한 위장관간질종양의 임상병리학적 특징 및 예후인자분석을 통해 발생위치에 따른 특징을 비교 분석하는 데 있다.

<방법> 서울대학교병원에서 1996년부터 2010년까지 수술적 절제를 시행한 297명의 상부위장관에 위치한 위장관간질종양 환자를 후향적으로 분석하였다. 이 중 위장에 발생한 환자는 각 196명 (66.0%), 소장 61명 (20.5%), 십이지장 40명 (13.5%)이었다.

<결과> 십이지장, 소장, 위장에 발생한 위장관간질종양 환자의 5년 생존율은 66.6%, 80.8%, 그리고 91.0% 순이었다 (p = 0.002). 단변량 분석을 통한 예후인자로는 남성 (5년생존률 82.9 대 89.6%, p = 0.036), R2 절제 (5년생존율 36.7 대 90.5%, p < 0.001), 술 전 낮은 혈색소 농도 (< 12 mg/dl) (5년생존율 76.9 대 95.0%, p = 0.002), 진행된 T 병기 (5년생존률 T4 69.1, T3 87.1, T2 95.3, T1 100%, p < 0.001), 높은 유사분열수 (> 5/ 50 HPFs) (5년생존율 75.7 vs. 96.9%, p < 0.001), 점막 침윤 (5년생존율 75.8 대 93.0%, p = 0.002), 동반된 괴사 여부(5년생존율 74.9 대 92.2%, p = 0.002), 동반된 점막궤양 (5년생존율 80.0 대 89.4%, p = 0.034), 그리고 동반된 S100 (5년생존율 59.5 vs. 91.9%, p = 0.003)이 있었다. 다변량분석을 통한 독립 예후인자로는 남성 (HR = 7.196, p = 0.043), R2 절제 (HR = 21.820, p = 0.019), 그리고 동반된 S100 (HR =15.622, p = 0.023)이 밝혀졌다. 추가적으로, 크기 증가 (HR

= 3.895, p = 0.061), 점막 침윤 (HR = 4.448, p = 0.073), 술 후 보조적 imatinib 치료를 하지 않은 경우 (HR = 2.683, p = 0.060)는 통계적으로 경계선에 위치한 독립 예후인자였다. 십이지장과 소장에 발생한 위장관간질종양에 한해 실시한 세부군분석에서는, 동반된 epitheloid 세포 (5년생존율 61.5 대 87.2%, p = 0.009), 그리고 PDGFRA 면역염색화학 양성(5년생존율 36.4 대 77.2%, p = 0.043)이 예후인자로 추가되었다. 재발빈도에 따른 위험도분석에서는 십이지장을 포함한 소장에 발생한 위장관간질종양의 재발률이 위장에 발생한 그것에 비해 위험도가 유의하게 높았다. (42.2% 대 13.0%, p < 0.001).

<결론> 십이지장과 소장에 발생한 위장관간질종양은 위장에 발생한 종양에 비해 임상적, 병리학적, 면역화학적 특징이 서로 상이하다. 따라서 십이지장 및 소장에 발생한 위장관간질종양은 악성의 위험도가 상대적으로 낮다고 하더라도 적극적인 수술적 절제가 필요하다

주요어: 위장관간질종양, 임상병리학적 특징, 예후인자

학번: 2010-23706